REMARKS/ARGUMENTS

Claims 1, 3-5, 7-8, 10, 24-25, and 27-32 are pending in the application. Claims 1, 5, and 10 have been amended to remove the reference to HIV infection. New claims 29-32 have been added drawn to preventing or treating an HIV infection. Support for the new claims can be found in the specification, at least on pages 7-9, as well as in the original claims. No new matter has been entered by amendment. Reexamination and reconsideration of the claims in view of the amendments and the following remarks are respectfully requested.

The amendments were not presented earlier because Applicant felt that they were not necessary to overcome the rejection. However, to further prosecution, the claims have been amended. No new matters are raised by the amendments. New claims 29-32 have been added to cover the embodiment that was deleted from claims 1, 5, and 10. Accordingly, the amendments should be entered.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

New claims 23 and 26 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. This rejection has been obviated by amendment. The examiner objected to the reference in the claims to an immune system disorder comprising HIV infection. The examiner indicated that HIV infection is not an immune system disorder. The claims have been amended to remove the reference to HIV infection. It appears that claims one and five should have been included in this rejection and accordingly have also been amended. Therefore, the rejection of claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 1, 3-5, 7, 8, 10, and 23-28 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

The present invention was based on a discovery by the present inventor that LPS binds to and activates A_1 adenosine receptors on human pulmonary artery endothelial cells (PAECs). Since the filing of the present application, this work was published in the *Journal of Endotoxin*

Research. A copy of the article was submitted with Applicant's previous response. The paper concluded that lipopolysaccharide (LPS) binds to and activates A_1 adenosine receptors on human pulmonary artery endothelial cells. The work was the first report to suggest the presence of A_1 adenosine receptors on human PAECs. It was also the first report to suggest that LPS binds to and activates A_1 adenosine receptors on human PAECs to induce the release of IL-6 and TXA_2. This finding is significant to the present invention as LPS has been reported as a potent stimulator of the expression of HIV-1 in monocytes and macrophages. As noted in the Background of the present specification, Tanaka *et al.* (2000) *AIDS* 14:1299 report that HIV-1 gene expression was activated 10 – 20 fold by LPS and serum p24 Gag protein levels reached 400 pg/ml, similar to those in the serum of AIDS patients.

The discovery that LPS binds to and activates A_1 adenosine receptors indicates that the effects of LPS on the expression of HIV-1 in monocytes and macrophages may be mediated by A_1 adenosine receptors and P_{2X} purinoceptors. It is this discovery that has led to the conclusion that the administration of compositions comprising A_1 adenosine receptor antagonists and/or P_{2X} purinoceptor antagonists, or a combination thereof, can prevent or inhibit immune system disorders. The Examiner is again referred to the Wilson and Batra (2002) *J. Endotoxin Res.* 8:263-271 article as the basis for this conclusion. Accordingly, based on the current knowledge in the field regarding the potential role of A_1 adenosine receptors in HIV infection (e.g., in HIV antigen presentation, HIV entry, and HIV replication in macrophages, etc.) and in other immunodeficiency diseases, the skilled artisan would not view the claims as lacking enablement. Similarly, as discussed in Applicant's previous response, the research supports a significant role for P_{2X} purinoceptors in immunodeficiency diseases, including HIV infection, AIDS, and ADA SCID.

The Examiner indicates that the disclosure fails to adequately address a number of factors. First, the Examiner indicates that adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) results from a genetic defect in the ADA gene. As the Examiner is aware, there are several forms of SCID. One of the forms is linked to a deficiency of the enzyme adenosine deaminase (ADA). Other causes of SCID are caused by a variety of other defects. The defining characteristic for SCID is a severe defect in T cell production and

function, with defects in B-lymphocytes as a primary or secondary problem and, in some genetic types, in NK cell production as well. A_2 adenosine receptors are present on human B and T lymphocytes. A_{2a} receptors have been identified as the predominately expressed subtype of adenosine receptors in T cells. The accumulation of adenosine and of dioxyadenosine in the absence of adenosine deaminase activity results in lymphocyte depletion and in ADA SCID. SCID patients have also been found to have an increased intracellular concentration of ATP and elevated levels of plasma adenosine implicating that modification through adenosine receptors may be beneficial in treatment therapies.

Second, the Examiner indicates that it is not readily manifest that A_1 adenosine receptor antagonists or P_{2X} purinoceptor antagonists would be efficient at inhibiting viral replication by reducing the viral burden associated with HIV infection. However, the inventor's discovery, as discussed above, that LPS binds to and activates A_1 adenosine receptors indicates that adenosine receptor antagonists and/or P_{2X} purinoceptor antagonists can prevent or inhibit immune system disorders. The Examiner is discounting the nexus provided by the inventor on LPS involvement in the claimed disorders.

Third and fourth, the Examiner indicates that the disclosure fails to provide any working embodiment demonstrating that ADA SCID was effectively treated with A_1 adenosine receptor antagonists or P_{2X} purinoceptor antagonists. However, the Examiner is reminded that working examples are not required to enable an invention. In the present case, Applicant has listed antagonists that can be used in the practice of the invention. See, the specification, pp. 10-13. All that is required is the administration of a suitable antagonist, as listed in the specification, to a patient. Accordingly, Applicant has taught how to make and use the invention and the rejection should be withdrawn.

Fifth, the Examiner indicates that the state of the art as it pertains to the treatment of ADA SCID has been unpredictable. The Examiner cites the gene therapy trials as an example of the unpredictability. However, gene therapy trials are a far cry from the administration of an antagonist. It is within the skill of the art to formulate an antagonist as set forth in the present application and administer it to treat ADA SCID.

Sixth, the Examiner indicates that the state of the art as it pertains to the generation of HIV antivirals is unpredictable. The Examiner indicates that there is nothing to suggest that the antagonist of the invention would effectively inhibit viral replication. However, Applicant has explained the nexus between the therapies of the invention and HIV mechanisms and has referred the Examiner to a publication by the inventor. Accordingly, without any evidence that the invention would not work as claimed, this rejection should be withdrawn.

Lastly, the Examiner indicates that the disclosure fails to provide sufficient guidance pertaining to the structures and binding activities of receptor antagonistic antibodies. The Examiner is reminded that Applicant does not have to teach what is well known in the art. As indicated on page 12 of the specification, methods for making antibodies are well known in the art. The specification then provides examples of antibodies that can be used in the practice of the invention. Furthermore, the Examiners referred to WO Publication WO 2007/063539 drawn to therapeutic uses of A_3 adenosine receptor antibodies. There are numerous references of monoclonal antibodies to adenosine receptors in the art. Accordingly, the Examiner's statements have no merit and the rejection should be withdrawn.

The Examiner has further discounted the specification and the references cited by the Examiner in support of the application. Applicant repeats the arguments made in the previous response that research implicates A_1 adenosine receptors and P_{2X} purinoceptors in immunodeficiency diseases such as HIV infection, AIDS, and ADA SCID. A_1 adenosine receptors are expressed on human immune cells and antigen-presenting cells (APCs), including dendritic cells, monocytes, macrophages, lymphocytes, peripheral blood mononuclear cells, and neutrophils. Both adenosine and HIV infection lead to a decrease in expression of CD4 on the surface of T cells, and HIV-mediated decreases in CD4 expression are considered to be an adenosine receptor-related phenomenon. See Sarzynska (2003) *J. Biomol. Structure Dyn.* 20:849; and Sipka *et al.* (1988) *Acta Biochim. Biophys. Hung.* 23:75-82. Regarding Sarzynska, the Examiner's statements goes beyond the teachings of the reference. The Examiner states that the "virus does not normally enter cells through a genomic RNA/cellular receptor interaction." (Office Action, page 5). However, this reference does not discount the possibility that HIV may enter cells by interacting with an A1 adenosine receptor via its "adenosine rich-loop."

Furthermore, with respect to Spika (1988), the Examiner notes that "Spika (1988) stated that A2 receptor stimulation, NOT antagonism, reduced HIV-related cytopathicity *in vitro*." (Office Action, page 5). The Examiner is correct in that the inhibitory effect of adenosine on CD4 and HIV expression is most likely via activation of A2 adenosine receptors by adenosine. This finding is not counter to the teachings of the present invention. In fact, by blocking the A1 adenosine receptor, the A2 adenosine receptor anti-inflammatory effect, i.e. inhibition of ICAM-1 expression (and thus specifically the interaction of PBMCs and lymphocyte cell-cell interaction by ICAM), is enhanced. That is, an A1 adenosine receptor antagonist enhances the A2 adenosine receptor inhibitory effect of adenosine.

In addition, HIV contains a polyadenylated 3′ end that can interact with adenosine receptors on human leukocytes. *Id.* Entry of HIV into target cells is dependent on interaction of a viral envelope glycoprotein with CD4 and one or more G protein-coupled receptors (e.g., adenosine receptors). See McElhinny *et al.* (1995) *J. Virol.* 69:1500-1509; Asin *et al.* (1999) *J. Virol.* 73:3893-3903; and Unutmaz *et al.* (1998) *Semin. Immunol.* 10:225-236. With respect to McElhinny (1995), the Examiner notes that the reference does not specifically state that activation of A1 adenosine receptors produces activation of NF-kB. However, LPS activates NF-kB and LPS binds to A1 adenosine receptors.

With respect to Unutmaz (1998), the examiner states that the virus does not regularly or frequently utilize G-protein coupled receptors. In fact, according to Unutmaz, the chemokine receptors, CCR5 and CXCR4, are GPCRs. However, based on the references provided including the teaching that LPS affects HIV replication in monocytes and macrophages and LPS binds to and activates A1 adenosine receptors, the teachings provide evidence that HIV utilizes another GPCR, i.e., the A1 adenosine receptor.

Moreover, it is well known in the art that HIV replicates in the absence of cytotoxicity, escapes surveillance by the immune system, and spreads via cell-to-cell contact. Researchers further postulate that persistence of HIV in human macrophages is dependent on NF-κB expression. *Id.* Lipopolysaccharide (LPS), which binds to and activates A_1 adenosine receptors (Wilson and Batra (2002) *J. Endotoxin Res.* 8:263-271), activates nuclear translocation of NF-κB, stimulates expression of HIV in monocytes and macrophages, induces HIV expression in

transgenic mice, and increases expression of HIV receptors on CD4+ T cells. See Sweet and Hume (1996) J. *Leuk. Biol.* 60:8-26; Pomerantz *et al.* (1990) *J. Exp. Med.* 172:253-261; Tanaka *et al.* (2000) *AIDS* 14:1299-1307; and Juffermans *et al.* (2000) *Blood* 96:2649-2654.

Accordingly, based on the current knowledge in the field summarized above regarding the potential role of A_1 adenosine receptors in HIV infection (e.g., in HIV antigen presentation, HIV entry, and HIV replication in macrophages, etc.) and in other immunodeficiency diseases, the skilled artisan would not view the claims as lacking enablement.

Similarly, research supports a significant role for P_{2X} purinoceptors in immunodeficiency diseases, including HIV infection, AIDS, and ADA SCID. P_{2X} purinoceptors are expressed on human immune cells such as dendritic cells, macrophages, and T cells and are involved in antigen presentation (e.g., on dendritic cells), cell-to-cell communication and fusion (e.g., via macrophages), and cytotoxicity and apoptosis (e.g., via T cells). See Di Virgilio *et al.* (2001) *Blood* 97:587-600; Apasov *et al.* (1995) *Immunol. Rev.* 146:5-19; and Coutinho-Silva *et al.* (1999) *Am. J. Physiol.* 276:C1139-C1147. Furthermore, as described above, LPS activates nuclear translocation of NF-κB and stimulates expression of HIV in monocytes and macrophages. This LPS-induced activation of NF-κB and the resultant cellular signaling events are inhibited by P_{2X} purinoceptor antagonists, strongly supporting the involvement of P_{2X} purinoceptors in immunodeficiency diseases. See Guerra *et al.* (2003) *J. Endotoxin Res.* 9:256-263. Copies of all of the above references were previously submitted to the Examiner for consideration.

The Examiner fails to appreciate that the references support the scientific principle on which the invention is based. That is, the discovery of A_1 adenosine receptors on human PAECs and the report that LPS binds to and activates A_1 adenosine receptors on human PAECs. Thus, it is believed that A_1 adenosine receptor antagonists will directly affect viral entry and replication in monocytes, macrophages, and lymphocytes.

Accordingly, in view of the above remarks, Applicant respectfully requests that the rejection of the claims for lack of enablement be withdrawn.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejection of the claims under 35 U.S.C. §112, first and second paragraphs, and to not apply these rejections to the newly submitted claims 29-32. In any event, the Examiner is respectfully requested to consider the above remarks and to enter the claim amendments for the purposes of further prosecution. ***Pursuant to 37 C.F.R. § 1.116 and MPEP § 714.12, any amendment that will place the application in condition for allowance may be entered after final rejection.*** Applicants believe that the present claim amendments place the claims in condition for allowance.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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LEGAL02/30762452v1